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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/037,519	01/03/2002	Daniel Benjamin	ORT-1550	7332

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EXAMINER	
COOK, LISA V	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/037,519	Applicant(s) BENJAMIN ET AL.	
	Examiner Lisa V. Cook	Art Unit 1641	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 January 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *25 January 2007*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *NONE*.
   Claim(s) objected to: *NONE*.
   Claim(s) rejected: *1-4*.
   Claim(s) withdrawn from consideration: *NONE*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Lisa V. Cook
2/21/07

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Continuation of 3. NOTE: The instant amendment to the claims raise issues under 112, 1st and 112, 2nd paragraphs. Previously the claimed method employed a synthetic peptide or peptide fragment wherein the synthetic peptide comprised or consisted of SEQ ID NO:3 or SEQ ID NO:4. The peptide fragment was not previously defined. Currently the claims utilize any fragment derived from SEQ ID NO:3 or SEQ ID NO:4. This new modification must be reconsidered with respect to new matter, indefiniteness, and written description. Applicant sites page 5 lines 1-19 as support for the new claim limitaions. However, the specification merely identifies synthetic peptides identified as SEQ ID NO:3 or SEQ ID NO:4. There are no other sequences, fragments, or derived fragments that would support the instant derived fragment language. The claims appear to be directed to compositions having at least one amino acid in common with SEQ ID NO:3 or SEQ ID NO:4, further employed to include any fragment containing said single amino acid. Accordingly, the amendment will not be entered .

Lisa. Cook
2/21/07

REQUEST FOR RECONSIDERATION

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A. The term "peptide fragment " in claim 1 is a relative term, which renders the claim indefinite. The term "peptide fragment" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear as to what if any fragments would maintain the required activity of the enhancing peptide. Accordingly, claim 1 and claims dependent on claim 1 (claims 2-4) are not clear. It is suggested that the term "peptide fragment" be removed or replaced with the actual peptide sequences in order to obviate this rejection.

Response to Arguments

Applicant contends that the term peptide fragment has been defined in the specification on page 5 lines 1-19. This argument was carefully considered but not found persuasive because the disclosure merely teaches peptide configurations having SEQ ID NO:3 or SEQ ID NO:4. There are no fragments exemplified or taught whereby the fragments would maintained the required enhancing capability necessary for the instantly claimed method. Accordingly, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4; and therefore the written description is not commensurate in scope with the claims drawn to "peptide fragments" or the enhancing peptide.

It is noted that claim 1 and dependent claims 2-4 have been interpreted to be drawn to methods utilizing the fragments of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4. However no such fragments have been shown in the specification nor exemplified in the method as claimed. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4; the skilled artisan cannot envision the detailed structure of the encompassed fragments and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polynucleotide itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus of nucleic acids by only their functional activity, does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus.

At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

No disclosure, beyond the mere mention of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4; is made in the specification. This is insufficient to support the claims drawn to the fragments thereof as provided by the Interim Written Description Guildlines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an isolated the sequence consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4; but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Response to Arguments

Applicant contends that the written description rejection is inadequate because it does not discuss the relevant level of skill and knowledge in the art for biological inventions. Applicant further argues that the peptide from which the peptide fragments are to be derived are set forth on page 5 of the specification. Therefore, it is well within the skill of one of ordinary skill in the art to make fragments of the peptides provided. This argument was carefully considered but not found persuasive because the specification must teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention. *In re Gardner*, 166 USPQ 138 (CCPA 1970).

Although SEQ ID NO:3 and SEQ ID NO:4 are taught the fragments therefrom (any 2 amino acid compositions found within these sequences) are not disclosed. For a reference to be enabling, it must place the disclosed subject matter in the possession of the public. *In re Brown*, 329 F.2d 1006, 141 USPQ 245, 249 (CCPA 1964).

Applicant also contends that the function of the fragments with in the instant method has been fully described. However, a description of what a material does rather what it is, usually does not suffice to provide adequate written description. *Univ. Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed Cir. 2004).

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 1-4 are rejected under 35 U.S.C.103(a) as being unpatentable over Biere et al. (US Patent #6,184,351) in view of Murray et al. (Society for Neuroscience Abstracts, Vol.26, No.1-2, 2000 – Abstract No.-84.10) and LeVine (Protein Science, 1993, 2, 404-410).

Biere et al. teach aggregation assays measuring aggregated human recombinant NACP/I-synuclein (column 3 lines 3-18 and Gene Core sequence search – result 2) in the present of a test compound.

In Biere's assay a pre aggregated alpha synuclein solution is added to the test sample and the change in fluorescent detection was measured at 280 nm - wavelength (as an indication of change in aggregation). See figure 3, column 2 lines 38-43, and column 8 lines 26-27. Multiple time points are measured to evaluate the change in aggregation (two different points in time). See figures 3 and 6, for examples.

The human recombinant NACP/I-synuclein composition taught by Biere et al. read on claims 3 and 4 because the claims recite compositions comprising residues 61-90 of alpha synuclein = SEQ ID NO:3 or SEQ ID NO:4. Therefore, the full length 140 amino acid NACP/I-synuclein of Biere et al. includes SEQ ID NO:3 and SEQ ID NO:4.

Biere et al. differ from the instant invention in not specifically teaching fluorescent detection with Thioflavin T (Thio T) at about 484 or 485.

However, Murray et al. disclose an aggregation system detecting compounds that inhibit alpha synucelin aggregation. The results were detected via Thioflavin T. Murray et al. taught that Thioflavin-T appeared to compete with test compounds to inhibit alpha syn aggregation and this could be monitored by the fluorometry assay but not by centrifugation. See abstract.

While, LeVine discloses that Thioflavin T's association with aggregates produces an enhanced emission at 482 nm (about 484 or 485). See abstract and page 405 1st column.

It would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention utilize Thioflavin-T at about 484nm or 485nm wavelengths, in the pre-aggregated alpha synuclein fluorescent detection method taught by Biere et al. because Murray et al. taught that Thioflavin-T appeared to compete with test compounds to inhibit alpha syn aggregation and this could be monitored by the fluorometry assay but not by centrifugation. See abstract. While, Levine taught that Thioflavin-T produced an enhanced emission at 482 nm. See abstract and page 405 1st column.

One of ordinary skill in the art would have been motivated to employ Thioflavin-T along with a test compound in a competitive method so that Thio T would serve not only as a positive marker (complete inhibition) but could also provide information of the test compounds interaction when other inhibitors are present. This would prove valuable in finding compounds to treating neurodegenerative illnesses exhibiting alpha syn aggregation (Parkinson disease/Alzheimer's disease). See Murray et al. abstract and LeVine page 404.

Response to Arguments

4. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., expedited aggregation of alpha synuclein) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Specifically, the claims merely require the aggregation of alpha synuclein in the presence of an alpha synuclein containing a synthetic peptide or peptide fragment derived from the synthetic peptide. Accordingly, the claims read on the prior art assays employing synthetic alpha synuclein peptides aggregates, which are evaluated for hundreds of hours or days. See Biere et al. (US Patent #6,184,351), column 4 lines 12-18 and column 9 – example 5 wherein artificial (synthetic) alpha synuclein mutants are employed *in vitro* aggregation assays.

Applicant contends that the claimed method utilizes *enhancing peptides* to expedite the rate of the alpha synuclein aggregation assay and the assays of the cited prior art are prolonged. This argument was carefully considered but not found persuasive because the cited art employs the same enhancing peptides in alpha synuclein aggregation assay (See Biere's wherein aggregated alpha synuclein solution is added to the test sample and the change in fluorescent detection was measured at 280 nm - wavelength (as an indication of change in aggregation). See figure 3, column 2 lines 38-43, and column 8 lines 26-27.

Applicants argue that the prior art does not teach assays that separately provide synthetic peptides or peptide fragments of 61-90 and 61-75 of alpha synuclein to enhance the aggregation of alpha synuclein solution. In other words the prior art does not employ the synthetic peptides in assay procedures for improved aggregation. This argument was carefully considered but not found persuasive because Biere et al. disclose enhanced aggregation with a synthetic construct designated H50Y/A53T. See column 4 lines 12-19 and lines 43-47. This H50Y/A53T comprises SEQ ID NO:3 of claims 3 and 4. See GeneCore Search Results dated December 9, 2004.

Applicant contends that the prior art does not teach separately adding enhancing peptides. However, Biere et al. teach the separate addition of mutant (synthetic) alpha synuclein as seeds to aggregation-competent, supersaturated solutions of wild type alpha synuclein in order to bypass the lag phase and cause rapid aggregation (enhancing peptides). See column 8 lines 34-42.

Also, the claims do not indicate a shorter time course for assay progression but merely read on an incubation of sufficient time to allow for a change in aggregation state (claim 1 step (b)). In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., shorter time course than the prior art methods) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The prior art is deemed to read on peptide fragments derived from SEQ ID NO:3 or SEQ ID NO:4 because the synthetic peptides taught by Biere et al. would contain at least 2 amino acid constructs from either SEQ ID NO:3 or SEQ ID NO:4. The rejection is maintained.

5. For reasons aforementioned, no claims are allowed.

6. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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